DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/08 has been entered.

The response filed on **8/18/08** presents remarks and arguments to the office action mailed on **2/6/08**. Applicants' request for reconsideration of the rejection of claims in the last office action has been considered.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

It is noted that No remarks are sent in.

Status of Claims

Claims 1-2, 4, 6-23 are pending. Claims 3 and 5 are cancelled and claims 22-23 are newly added.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4, 6-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for NK2 (saredutant) and NK3 (osanetant) for example, does not reasonably provide enablement for a very wide variation of neurokinin receptors antagonist and or co-administration of the wide variation as claimed in instant claim 6-7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

The nature of the invention: The instant invention pertains to a method of treating hot flashes in post menopausal women, or in male patient taking anti-androgen drug.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims 1-2, 4, 6-21 are deemed very broad since these claims reads on any NK2 or NK3 receptor antagonists and further in combination with any tachykinin receptor antagonists employed in the claimed methods of treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 1-2, 4, 6-21, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997).

In the instant case, "an NK2 and or NK3 receptor antagonist" and "a tachykinin receptor antagonist" recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. Thus, Applicants functional language at the points of novelty in claims 1-2, 4, 6-21,

fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph, since it fails to provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" *(General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus., visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the member's genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treating hot flashes in post menopausal women, or in

male patient undergoing anti-androgen treatment, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a postmenopausal woman) the *combination* of any compounds represented by "an NK2/NK3 receptor antagonist" and "a tachykinin receptor antagonist". See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions ($9^{med.}$ 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except for those particular compounds in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed method herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 4, 8-11 and 19-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. WO 99/09987 in view of Norheim et al. Clin. Endocrin. Metab, 1986:63 (3) Abstract Only further in view of Guthrie et al. Obstet. Gynecol. 1996; 88;437-442.

Shapiro teaches that tachykinin receptor antagonist NK-1, NK-2 and NK-3 are useful for the treatment of premenstrual or late luteal phase syndrome, see abstract, page 6, lines 1-5, lines 11-15 and 19-26 as required by instant claims 1-2 and 4. With regards to the dosage amount as required by instant claim 8, the reference teaches that the neurokinin receptor antagonist can be administered in a range of 0.1-500 mg/day,

see page 52, line 4 and page 56, lines 23-35. It is noted that NK-1 is the preferred antagonist used, however, since the reference teaches all these receptors can be used the dosage is assumed to be the same for the other neurokinin antagonist. The reference also teaches that these neurokinin antagonists are administered to a female patient as required by instant claim 9. The reference also teaches that the neurokinin antagonist are administered orally as a solid dosage form, intramuscularly etc , see page 51, lines 15-26 as required by instant claims 19 and 21 in a pharmaceutical composition and a pharmaceutically acceptable carrier, see same. Shapiro also teaches that PMS seems to be related to fluctuations in estrogen and progesterone, estrogen-progesterone imbalance, excessive aldosterone or ADH (see page 2 line 21-31). (Please note that when the specification was consulted, tachykinins receptor antagonist is inclusive of NK-1, NK-2 and NK-3).

Shapiro et al, fail to teach that these compounds are employed for neither the treatment of hot flashes nor the treatment in a post menopausal patient. For this reasons Norheim et al and Guthrie are introduced. Norheim for the teaching that tachykinins (also known as neurokinins are employed in treating patients experiencing flushing and hot flash induced by drug. Guthrie to show that hot flash is not only experienced by post menstrual but in patients with menstrual status.

Norheim et al. teach that tachykinins are involved with flushing see entire abstract. The reference also teaches that flushing was induced by the administration of drug pentagastrin as required by instant claim11-12.

Guthrie et al. teach in the study conducted on hot flashes, menstrual status and **hormone variation** that the frequency of hot flushes in a population sample of pre-, and postmenopausal women is associated with menstrual status. Further, Guthrie et al. teaches that the frequency of hot flashes is associated with a history of premenstrual complaints, see abstract and entire article.

From the reading of the instant specification it is noted that Applicant invention is inclusive of symptoms of hormonal variation. See page 3, lines 3-10.

One of ordinary skill in the art would have been motivated at the time the claim invention was made to employ the particular tachykinins/neurokinin receptor antagonist, identify which of the numerous neurokinins receptor antagonist 1-3 will be effective to treat hot-flash since the general teaching by Shapiro that NK-1, NK-2 and NK-3 are useful for the treatment of premenstrual or late luteal phase syndrome. Guthrie teaches that hot flashes is associated with a history of premenstrual complaints an association between menstrual status and post menopausal status and that the hormonal changes experience by both groups is hot flash. One of ordinary skill in the art also would have known that PMS is caused by hormonal changes of estrogen imbalance in the female patient.

Thus motivation of one of ordinary skill in the art to have reasonably expected that employing any NK-receptor antagonist be it NK1, NK-2 or Nk-3 would show a reasonable amount of success because these neurokinins or tachykinins have been employed to treat hormonal variation in menstrual patients. Hot flash is a hormonal variation, therefore one of ordinary skill in the art would have been motivated to

administer the same type of neurokinin/tachykinin antagonist and expect a successful result in doing so. Thus motivation to administer in post menopausal patients since hot flash in menopausal and hot flash in menstrual patients are assumed to be the same.

Claims 13-18 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. WO 99/09987 in view of Norheim et al. Clin. Endocrin. Metab, 1986:63 (3) Abstract Only further in view of Guthrie et al. Obstet. Gynecol. 1996; 88; 437-442 as applied to claims 1-2, 4, 8-11 and 19-21 above, and further in view of Edmonds-Alt et al. US 6,420,388 in view of Casper et al, Clinical Endocrin, 1985, 22;293-312 and Sukoff Rizzo et al. US 7,425,558 and further in view of Gollobin US 6,245,812 as evidence by Eisenberger, The New England J. of Medicine 1998, 339; 1036-1042 and Guang-Shing Cheng.

The above references are applied her below in their entirety. The references fail to teach the specific compounds as in instant claim 22-23 or a method of treating hot flash in a patient wherein the patient is a male patient undergoing an anti-androgen treatment.

Edmonds-Alt et al. teach administering a neurokinin receptor antagonist osenetant (see instant claim 23) in the treatment of diseases associated with noradrenergic dysfunction, see col. 1, lines 1-32.

Sukoff Rizzo et al. teach both saredutant and osanetant as compounds of noradrenergic and serotonin drugs employed for sexual dysfunction.

Casper is further introduced for the teaching that noradrenergic system is involved in menopausal flushes, see underlining page 8.

Gollobin teaches that flushing is caused by reduction of estrogen associated with natural menopause in women, but can also be induced by drugs and such drugs are anti-estrogens (tamoxifen) and leuprolide acetate. See col.1, lines 19-30 and col. 2, lines 54-63. Therefore regardless of the patient being female or male once these drugs are administered induce hot flash in the patient. As evidence by Eisenberger leuprolide acetate is administered to men for the treatment of prostate cancer. See entire document.

One of ordinary skill in the art would have reasonably expected that administering a NK-antagonist would be capable of treating symptoms due to estrogen fluctuation in women or a male following androgen-deprivation. Further, one of ordinary skill in the art would be motivate to administer osanetant because it is known in the art for the treatment of noradrenergenic dysfunction, wherein menopausal flushing is a known disease. Also as evidence by Cheng, women treated for hot flash experience improvement in sexual function when a noradrenergic (Paroxetine) was administered. See underlining. Therefore one of ordinary skill in the art would have been motivated to employ a neurokinin receptor (osanetant and or saredutant) that is known also for its noradrenergic function in the treatment of hot flash as taught by Edmonds-Alt et al because products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the

prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1 – 2, 4 and 6-23** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1, 9-10, 12-22** of U.S. Patent Application No. **09/879390** in view of Shapiro et al. WO 99/09987 (see supra). Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

Both sets of claims refer to treating hot flash in a female or a male patient and in a post menopausal patient. The composition for treatment as recited in instant claims **6-7** overlaps with the copending application claim **1**. The copending application fails to teach other NK receptor antagonist. Sharpiro is introduced to show that NK1, NK2 and NK3 are employed in the treatment of hormonal variation.

Even though the co-application is directed to only NK-1, one of ordinary skill in the art would have been motivated to employ the teachings of Shapiro wherein the tachykinin receptor antagonist NK-1, NK-2 and NK-3 are employed for hormonal variation. One such known hormonal variation is hot flash. One of ordinary skill in the art also would have known that PMS is caused by hormonal changes of estrogen imbalance in the female patient and therefore are part of the obvious variation of the copending application claims compared to the current application claims.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to 8whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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